UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,236	12/02/2003	Jennifer Lockridge	MBHB01-1735-B (400.140)	4026

20306 7590 12/11/2006

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,236	LOCKRIDGE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed September 20, 2006.

Claim 9 has been canceled. Claims 1 and 8 have been amended.

Claims 1-8 and 10-26 are pending in the instant application.

Claims 1-8 and 10-26 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

The previous Restriction Requirement made of record in the previous Office Action mailed March 20, 2006 is moot in view of Applicant's Amendment to the claims to cancel claim 9 and to remove reference to the term, "VEGF" in claim 1.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed March 20, 2006, claim 8 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment to the claim filed September 20, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claim to insert the full name of the growth factor receptor.

In the previous Office Action mailed March 20, 2006, claims 1-8 and 10-26 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is withdrawn** in view of Applicant's Amendment to the claims filed September 20, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite, "SEQ ID NO:14".

In the previous Office Action mailed March 20, 2006, claims 1-8 and 10-26 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of locally administering to a cell or tissue *in vitro*, a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor, does not reasonably provide enablement for a method of locally administering to a cell or tissue *in vivo* (whole organism), a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed March 20, 2006.

Applicant is reminded that the instant specification at page 21, last paragraph discloses, "The term "double-stranded RNA" or "dsRNA" as used herein refers to a double-stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA"". Given Applicant's disclosure, the Examiner will use the terms double stranded RNA, double-stranded RNA capable of RNA interference, and siRNA interchangeably. It is also noted that throughout the entire specification, the method of locally administering to a cell or tissue a double-stranded RNA complementary to a

nucleotide sequence of a VEGF receptor is intended for the purpose of inhibiting the gene expression of a VEGF receptor or is intended for the purpose of treating a disease in a human (see for example the instant specification at page 6, second full paragraph; page 7, paragraphs 4 and 5; page 10, fourth and sixth paragraphs; and page 11, last full paragraph).

Response to Arguments

In response to this rejection, Applicants argue that the specification teaches how to design double stranded nucleic acids that target a VEGF receptor. Applicants contend that the specification teaches how to use the double stranded nucleic acids for *in vivo* administration. Applicants point the Examiner the instant specification at pages 33, 34-48, and 46-55, and to U.S. Provisional Application No. 60/393,796 at pages 68-75.

This argument and contention have been fully considered but is not found persuasive because first, the instant application has not been afforded priority to U.S. Provisional Application No. 60/393,796 because support for the claims, drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14, cannot be found in Provisional Application No. 60/393,796. Instead, the instant claims have been afforded priority to December 2, 2003, which is the filing date of the instant application. For further explanation, see the new 35 U.S.C. 112, first paragraph rejection against claims 1-8 and 10-26 for new matter as detailed below in this Office

Action. Second, and as discussed in the previous Office Action mailed March 20, 2006, the field of dsRNA therapy, including double-stranded RNA molecules capable of RNA interference or siRNA, at the time the instant invention was made, does not provide guidelines by which double stranded nucleic acid molecules capable of RNA interference can be routinely delivered to generally any cell type *in vivo* (whole organism) to inhibit gene expression or treat a disease in a human as contemplated in the instant specification. Thus, the instant claims are not enabled over the breadth of the scope claimed.

Applicants also argue that the instant specification has adequately disclosed a correlation between the function and structure of the claimed invention by describing the role of VEGF receptor in angiogenesis, including ocular angiogenesis and tumor angiogenesis. Applicants contend that because the instant specification teaches that abrogation of VEGF receptor gene expression results in inhibition of angiogenesis, and that double stranded nucleic acids can be used to down regulate gene expression, the specification enables one of skill in the art to practice the claimed invention by describing how to design, synthesize, and administer double stranded nucleic acid molecules targeting VEGF receptor.

This argument and contention have been fully considered, but are not found persuasive because, as argued in the previous Office Action mailed March 20, 2006, *in vivo* delivery of ribozyme nucleic acids are generally not predictive of delivery of double stranded nucleic acids capable of RNA interference, particularly siRNA molecules, due to differences in the duplex nature of the siRNA molecule.

The specification discloses the pharmacokinetics and tolerability of an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, in a Phase I/II trial. The specification goes on to disclose that the ANGIOZYME™ interfered with the menstrual cycle of one of the patients in the Phase I/II trial, perhaps by inhibiting neovascularization of uterine tissue. Based on these results, the specification contemplates that ANGIOZYME™ and/or other nucleic acid molecules, including double stranded nucleic acids capable of RNA interference, could be locally administered to other tissues or cells *in vivo*. The issue is that the specification does not demonstrate any correlation with the pharmacokinetics and tolerability of an antiangiogenic VEGF receptor ribozyme, with the administration of a VEGF receptor double stranded nucleic acid capable of RNA interference in a mammalian subject *in vivo* (whole organism). The specification does not present any examples wherein any double stranded RNA capable of RNA interference, siRNA or otherwise, was delivered to cells *in vivo* (whole organism). The Examiner cannot find a single example in the instant specification wherein a VEGF receptor double stranded nucleic acid capable of RNA interference was administered to a cell or tissue in a whole animal. Thus, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants finally argue that using the teachings of the instant application, Applicant has practiced the claimed invention and this reduction to practice demonstrates that double stranded nucleic acids can be administered to a whole animal (*in vivo*). Applicants contend that co-pending US Patent Applications demonstrate the

inhibition of ocular angiogenesis using double stranded siRNA molecules targeting VEGFR1 RNA and post-filing data indicates the instant specification fully enables the claimed invention.

This argument and contention have been fully considered but are not found persuasive. The specification provides examples wherein an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, is delivered to patients in a Phase I/II trial, however, as discussed in the previous Office Action mailed March 20, 2006, delivery of ribozyme nucleic acids are generally not predictive of delivery of double stranded nucleic acids capable of RNA interference, particularly siRNA molecules *in vivo*, due to differences in the duplex nature of the siRNA molecule. Furthermore, the specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver a double-stranded RNA molecule capable of RNA interference to generally any target cell or tissue *in vivo*. Regardless of the fact that co-pending US Patent Applications or post-filing data demonstrate the inhibition of ocular angiogenesis using a double-stranded siRNA molecules targeting VEGFR1 RNA, at the time the invention was made, the delivery and therapeutic use of double stranded nucleic acids capable of RNA interference, including siRNA molecules, was highly unpredictable.

Applicant is reminded that the instant claims have been afforded priority to December 2, 2003, which is the filing date of the instant application. As discussed in the previous Office Action mailed March 20, 2006, the field of double-stranded nucleic acid therapy, at the time the instant invention was made does not provide guidelines by

which double stranded nucleic acids capable of RNA interference can be routinely delivered to generally any cell type *in vivo* as broadly encompassed by the claims.

Thus, it is maintained that the prior art at the time of Applicants' filing would not enable the therapeutic use of double stranded nucleic acids capable of RNA interference. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of the pharmacokinetics and tolerability of an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, in a Phase I/II trial enough to overcome the unpredictability and challenges of delivering a VEGF receptor double-stranded nucleic acid capable of RNA interference *in vivo*, as exemplified in the references and discussions found in the previous Office Action mailed March 20, 2006. Therefore, due to the broad scope of the methods claimed, the state of the art of using double stranded nucleic acids capable of RNA interference therapeutically, particularly siRNA, the level of unpredictability of *in vivo* (whole organism) methods of using siRNA, the lack of specific guidance for the *in vivo* application of double-stranded nucleic acids capable of RNA interference and methods for *in vivo* delivery, and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods claimed commensurate in scope with these claims.

Applicant's Amendment necessitated the new issues and new grounds of rejection presented below:

Priority

The instant claims have been amended and are currently drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14. The Examiner would like to point out that Applicants contend that SEQ ID NO:14 represents GenBank entry NM_002019 as disclosed in the instant specification at page 6, line 8 (see Applicant's Remarks filed September 20, 2006 at page 1, titled "The Claim Amendments"). At the outset, it is immediately noticed that the sequence of GenBank Accession Number NM_002019 contains thymine residues, where SEQ ID NO:14 of the instant application has substituted the thymine residues with uracil residues.

It is noted that in the previous Office Action mailed March 20, 2006, the claimed invention was afforded priority to U.S. Provisional Application No. 60/334,461, filed November 30, 2001 because no other parent application(s) for which Applicants claim benefit had support for the terms "RNA interference" or "RNAi".

Now then, considering the claims as currently amended and referring to Provisional Application No. 60/334,461, it is noted that the Application has support for GenBank Accession Number NM_002019 (see page 55), however, the Application does not have support for the sequence of SEQ ID NO:14 as disclosed in sequence listing of the instant invention.

In summary, the instant claims have been afforded priority to the filing date of the instant application, which is December 2, 2003 because none of the parent applications, including Provisional Application No. 60/334,461, have support for the claims as now amended.

If Applicants believe that they are entitled to an earlier priority date, the Examiner urges Applicant to specifically point where support can be found for the sequence of SEQ ID NO:14 or the sequence of GenBank Accession Number NM_002019 in any other applications Applicants claim priority to.

Specification

The amendment filed September 20, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the Amendment filed September 20, 2006, Applicants have submitted a new sequence listing in which SEQ ID NO:14 has been added. Applicants contend that SEQ ID NO:14 represents GenBank entry NM_002019 as disclosed in the instant specification at page 6, line 8 (see Applicant's Remarks filed September 20, 2006 at page 1, titled "The Claim Amendments"). It is noted that the sequence of GenBank entry NM_002019 was submitted and made of record on the information disclosure statement filed December 2, 2003. Comparing GenBank entry NM_002019 with SEQ ID NO:14 of the instant application, it is immediately noticed that the sequence of the Accession Number

contains thymine residues, where SEQ ID NO:14 has substituted the thymine residues with uracil residues.

In summary, the instant specification does not appear to support GenBank Accession Number NM_002019. Furthermore, GenBank Accession Number NM_002019 and newly submitted sequence SEQ ID NO:14 are not the same sequence since one is a DNA sequence and the other is an RNA sequence. In this regard, SEQ ID NO:14 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14. It is noted that SEQ ID NO:14 was added to the sequence listing in the Amendment filed September 20, 2006. The Examiner would like

to point out that Applicants contend that SEQ ID NO:14 represents GenBank entry NM_002019 as disclosed in instant specification at page 6, line 8 (see Applicant's Remarks filed September 20, 2006 at page 1, titled "The Claim Amendments"). It is noted that GenBank entry NM_002019 was submitted and made of record on the information disclosure statement filed December 2, 2003. Comparing GenBank entry NM_002019 with SEQ ID NO:14 of the instant application, it is immediately noticed that the sequence of the Accession Number contains thymine residues, where SEQ ID NO:14 has substituted the thymine residues with uracil residues.

In summary, the instant specification does not appear to support GenBank Accession Number NM_002019. Furthermore, GenBank Accession Number NM_002019 and newly submitted sequence SEQ ID NO:14 are not the same sequence since one is a DNA sequence and the other is an RNA sequence. In this regard, SEQ ID NO:14 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
November 30, 2006

SEAN McGARRY
PRIMARY EXAMINER
AU 1635